CASE REPORTS

# Severe refractory hypercalcaemia in HTLV-1 infection

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In hypercalcaemia, exclusion of common causes such as hyperparathyroidism or disseminated malignancy is straightforward. Matters become more difficult when no obvious cause can be found. A rare cause of refractory hypercalcaemia is adult T-cell leukaemia/lymphoma (ATLL) induced by human T-cell leukaemia virus type-1 (HTLV-1).

## CASE HISTORIES

### Case 1

A 61-year-old Jamaican man was admitted with a 3-day history of generalized weakness. His wife, also originally from Jamaica, had died from ATLL 2 years previously. Serum calcium was 4.53 mmol/L (reference range 2.2–2.6), phosphate 1.62 mmol/L (0.8–1.5), alkaline phosphatase (ALP) 73 IU/L (40–135) and white cell count (WCC) $6.6 \times 10^9$/L (3.9–11) with lymphocyte count $3.26 \times 10^9$/L (1–4). He was treated with intravenous fluids, diuretics and pamidronate. Serum parathyroid hormone (PTH) was 0.2 pmol/L (1.3–7.6), urinary Bence Jones protein negative, normal serum angiotensin converting enzyme (ACE) level and plasma electrophoresis, and lactate dehydrogenase (LDH) 727 U/L (110–460). Blood was sent for HTLV-1 serology. A blood film showed 'some abnormal lymphocytes'; bone marrow appeared normal and was sent for phenotyping. Despite treatment with intravenous fluids, diuretics and pamidronate his serum calcium climbed to 5.08 mmol/L. Steroids were begun and further pamidronate was administered. These measures brought down his calcium level for one 1-week, but it again climbed to 5.11 mmol/L. HTLV-1 serology was reported as positive, and it emerged that his wife had been HTLV-1-positive. On the assumption that he had HTLV-1-induced ATLL, he was started on zidovudine and α-interferon. He remained hypercalcaemic, and high-dose chemotherapy was administered. He is currently normocalcaemic and well.

### Case 2

A Ghanaian woman of 33 attended with a 2-week history of fatigue, diffuse abdominal pain, constipation and nausea. She had lived in the UK for 23 years but frequently returned to Ghana. On examination she had cervical lymphadenopathy. Serum calcium was 4.23 mmol/L, phosphate 1.38 mmol/L, ALP 86 IU/L and WCC $7.8 \times 10^9$/L with a lymphocyte count of $0.64 \times 10^9$/L. 2 weeks previously her serum calcium had been 2.7 mmol/L when checked by her general practitioner. She was treated with intravenous fluids, diuretics and intravenous pamidronate. Further investigations revealed a PTH of 0.44 pmol/L, negative urinary Bence Jones protein, normal serum ACE and plasma electrophoresis and negative Mantoux test. LDH was raised at 4990 U/L. Ultrasonography confirmed cervical and intra-abdominal lymphadenopathy. Blood was sent for HTLV-1 serology and a lymph node biopsy was performed. Because of deteriorating renal function and cardiac failure the patient was admitted to intensive care. Serum calcium remained raised despite treatment with intravenous fluids, diuretics, steroids and further pamidronate. Examination of the lymph node revealed high-grade T cell anaplastic lymphoma, and she was started on chemotherapy. She developed multiorgan failure and died 26 days after admission. Her HTLV-1 serology was reported as positive.

### Case 3

A 74-year-old Jamaican woman was admitted with a 3-week history of an enlarging right parotid swelling and fatigue but no weight loss or fevers. She had a $6 \times 4$ cm parotid mass and inguinal lymphadenopathy. Serum calcium was raised at 3.39 mmol/L, phosphate 1.68 mmol/L, ALP 184 IU/L and WCC $34.3 \times 10^9$/L with lymphocyte count $22.1 \times 10^9$/L. Blood film showed lymphocytosis suggestive of peripheral T-cell lymphoproliferative disease. CT of the neck and thorax revealed a mediastinal mass consistent with lymphoma and some narrowing of the trachea, with extensive cervical lymphadenopathy. She was treated with intravenous fluids, diuretics, steroids and intravenous pamidronate. HTLV-1 serology was requested. Lymph node biopsy showed ATLL. She deteriorated during chemotherapy, developed multiorgan failure, and died 29 days after admission. HTLV-1 serology was reported as positive.

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## COMMENT

ATLL was first described as a distinctive malignancy of mature CD4+ (helper) T cells, when a high prevalence was reported in south-west Japan. It was subsequently identified in West Indian immigrants in the UK, and human T-cell leukaemia virus type-1 (HTLV-1) is now known to be the causative agent of ATLL[1]. Some 10–20 million people world-wide are infected with HTLV-1, which is endemic to Japan, the Caribbean, Central and South America and Africa where the seroprevalence is 1–20%. The estimated lifetime risk of developing ATLL in a person positive for HTLV-1 is 2–5%, with a latency of 20–30 years.

ATLL occurs in adults, with a median age at onset of 58 years, and is classified into four clinical subtypes—smouldering, chronic, lymphoma and acute. Patients with the first two subtypes rarely develop hypercalcaemia. Acute type ATLL is the commonest and both acute and lymphoma types have a much poorer prognosis than the other two subtypes. Poor prognosis is further indicated by raised LDH and calcium and by a high WBC, with 50% survival of less than 6 months even with combination chemotherapy[2]. Treated with zidovudine and α-interferon, a small percentage of patients achieve longlasting remission[3].

The exact prevalence of HTLV-1 positivity is hard to assess, though the prevalence in Jamaicans over 70 has been estimated at 17.4% for women and 9.1% for men. The North London Blood Transfusion Service estimate a prevalence of 0.005% in their local blood donors, whilst a study of Afro-Caribbean blood donors suggested a prevalence of 0.1%[4]. The catchment area of the Central Middlesex Hospital has a high immigrant population (approximately 45% non-English origin). In a study from the Royal London Hospital, which also serves a large ethnic minority population, 12 cases of HTLV-1 associated disease were found over 5 years[5].

Hypercalcaemia is a common finding in the normal population and in hospital patients[6]. The approach to investigation is reviewed elsewhere[7]. Hypercalcaemia occurs in about 50% of patients with HTLV-1 induced ATLL, and, as in the three cases presented, attempts to control calcium levels may dominate the clinical course. The mechanism of hypercalcaemia associated with ATLL seems to be stimulation of bone resorption by the production of parathyroid-hormone-related peptide (PTH-rP), with ATLL cells constitutively expressing a large amount of PTH-rP mRNA[8].

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# Pathergy in non-Hodgkin lymphoma

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Pathergy is the development of a papulopustular lesion around a puncture site on the skin, 24–48 hours after the injection of a sterile substance[1]. The pathergy test is used in some parts of the world as a diagnostic criterion for Behçet's disease[2].

## CASE HISTORY

A man aged 24 reported low-grade fever for eight months, pain and swelling in the right leg and knee for about six months and pustular lesions over the lips, arms and genitalia for the past three months. During this period he had been in Saudi Arabia and had been admitted three times for the treatment of fever and abscesses. Culture of aspirates from the right knee joint had been negative; 40% of the white cells were lymphocytes, 60% neutrophils; protein 53 g/L. On admission to our hospital he was febrile and tachycardic. There was no palpable lymphadenopathy. Over the left forearm and right elbow there were raised ulcers with

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